Technology Assessment Program
Office of Patient Care Services

Bibliography*: Anemia in heart failure

*Selected, quality filtered, not subject to external review

Policy issue: VHA's Technology Assessment Advisory Group (TAAG) requested a review of transfusion in congestive heart failure. Exploratory searches for post-1990 research retrieved too few citations to support a focused review, encouraging expansion of our charge to a catalog of anemia-related systematic reviews for heart failure, which provides a comprehensive overview of the status of evidence.

Methods: TAP searched PubMed, INAHTA databases, Embase, and the Cochrane Library using "transfusion", "anemia", "hemoglobin", "hematocrit", and "iron deficiency" , all crossed with "heart failure".

Included: Systematic reviews and subsequently published eligible studies; comparative studies; and cost studies or economic evaluations in adults with heart failure and peer-reviewed published in English from 1990 to 2010.

Excluded:
- Narrative reviews, letters, and other publications lacking primary patient-based data and/or explicit methods descriptions.
- Articles judged unintelligible by at least two TAP staff.
- Inaccurately indexed or otherwise irrelevant to our charge.
- Laboratory or other pre-clinical studies.
- Primary studies already covered in systematic reviews.

Literature appraisal
The progression of epidemiologic studies, or the epidemiologic study cycle, confirming the existence and magnitude of an association between exposure and disease or intervention and outcome is well-documented (Ibrahim, 1985; Mausner and Kramer, 1985; Lilienfeld and Stolley, 1994; Muir Gray, 1997): it begins with observational, hypothesis-generating studies such as single case or case series reports, then on to cross-sectional (also known as survey, correlational, or ecological) studies, which ascertain exposure and disease in populations at the same point in time, then progresses through analytic, hypothesis-testing studies (case-control or cohort, from which relative risk or estimates can be calculated), and culminates in the randomized controlled trial confirming causality.

The systematic review synthesizing multiple primary studies provides an ultimate level of evidence, as do economic evaluations using efficacy data from reviews, and ideally collecting resource data during the course of randomized trials that also supplied causal evidence.

Systematic reviews
Systematic reviews (detailed below) qualify as reproducible science and their production requires a threshold level of available primary research. Published systematic reviews thus provide an immediately accessible overview of the general status of a body of research literature. Conversely, the lack of published high-quality systematic reviews indicates a corresponding lack of published research.

Cook (1995 and 1997) defines systematic reviews: "*Systematic reviews are scientific investigations in themselves, with pre-planned methods and an assembly of original studies as their "subjects". They synthesize the results of multiple primary investigations by using strategies that limit bias and random error…"*

The same authors further specify characteristics of systematic reviews and contrast them with traditional narrative reviews: the latter synthesize articles without reporting methods of selection or quality assessment criteria and thus do not qualify as reproducible unbiased science.

Systematic reviews:

- Ask a focused clinical question;
- Conduct a comprehensive search for relevant studies using an explicit search strategy;
- Uniformly apply criteria for inclusion and exclusion of studies;
- Rigorously and critically appraise included studies;
- Provide detailed analyses of the strengths and limitations of included studies.

Results: TAP's searches identified a total of 621 citations, of which 27 were retrieved for in-depth review. Of those, 18 articles (Table 1) met inclusion criteria and are abstracted in detail in Table 2. Table 3 lists subsequently published studies that would be eligible for inclusion in the Table 1 reviews. Table 4 lists in-progress clinical studies for anemia in CHF. Finally, Table 5 lists retrieved articles that were excluded from review and the reasons for exclusion.

Table 1. Overview of available systematic reviews and subsequently published eligible primary studies

Citation	Content	Setting
Transfusion for CHF		
Marik (2008)	RBC transfusion and morbidity/mortality in ICU patients: numbers/diagnosis not reported	Publication years 1966-2007
Anemia in CHF		
Ngo (Cochrane; 2010)	Erythropoeisis-stimulating agents (ESAs) for CHF patients with anemia	RCTs 1950-2008
He (2009)	Predictive value of anemia	-2007
Tehrani (2009)	Darbepoetin in CHF	1966-2008
Groenveld (2008)	Anemia and mortality in heart failure	-2007
Van der Meer (2008)	ESAs for anemia in CHF	-July 2008
Ngo (Cochrane; 2010)	ESAs with or without Iron	RCTs 1950-2008
Hill (Cochrane; 2009)	effect of transfusion thresholds on use of allogeneic and/or autologous blood or on clinical outcomes:	-2009
Jones (2005)	ESA: effects on LV hypertrophy and mortality	1985-2000
Smith (2006)	Renal impairment and outcomes in HF	-May 2005
Taylor (Cochrane; 2005)	Clinical service organization for HF	-July 2003

Citation	Content	Setting
Hill (Cochrane, 2000; updated 2009)	Strategies for guiding allogeneic RBC transfusion	1966-2004
Other reviews		
Felker(2009)	BNP- Vs symptom-guided therapy	1996-2009
Subsequently published review-eligible		
Adams (2009)	Prevalence and correlates of anemia in unselected HF patients	Registry: UA academic medical centers and community clinics
Garty (2009)	Transfusion in hospitalized HF patients	Israel
Pfisterer (2009)	TIME-CHF trial	BNP- Vs symptom-guided therapy
Tehrani (2009a)	Predictive value of anemia	HF with preserved systolic function
Go (2006)	Hb, CKD, and risks of death/hospitalization in CHF	Kaiser-Permanente

Table 2. Abstracted details of Table 1 reviews

Citation	Design/methods	Results/Conclusions
Ngo (Cochrane; 2010)	**Benefits and risks of ESA for CHF patients with anemia:** • Multiple databases, 1950-Oct 2008; • RCTs of any ESA, with or without iron therapy; • No language restrictions; • Outcomes: exercise tolerance; hemoglobin level; NYHA functional class, QoL; , LVEF; B-type natriuretic peptide; CHF-related hospitalizations; all-cause mortality; adverse effects. • Cochrane quality assessment and meta-analysis	**11 studies (794 subjects):** • Overall quality moderate: 9 trials placebo controlled but only 5 blinded; small sample sizes and limited duration; • ESA improved exercise duration: by 96.8 seconds (CI, 5.2-188.4; p =0.04); 6-minute walk distance by 69.4 meters (CI, 17.0-121.7l p = 0.009); • Other benefits: peak VO_2 (+2.29 mL/kg\/min; p =0.007); NYHA class (-0.73; p<0.001); LVEF (+5.8%; P<0.001); B-type natriuretic peptide (-226.99pg.ml: p<0.001); QoL indicators; hemoglobin(+9.98g/dL; P<0.0001); hospitalizations (RR, 0.62; CI, 0.44-0.87); and all-cause mortality (RR, 0.61; CI, 0.37-0.99); • No increase in adverse events. **Conclusions:** *"Meta-analysis of small RCTs suggests that ESA treatment in patients with symptomatic CHF and mild anemia (hemoglobin > 10g/dL) can improve anemia and exercise tolerance, reduce symptoms and have benefits on clinical outcomes. Confirmation awaits well-designed studies with careful attention to dose, hemoglobin treatment target and associated iron therapy."*
Felker (2009)	**Does titration of therapy based on BNP measurement improve mortality in chronic heart failure?** • Multiple databases and meeting proceedings, 1996-2009; • Prospective RCTs enrolling patients with heart failure and titrating medical therapy by circulating BNP levels Vs parallel control group; reporting all-cause mortality; • No language or publication restrictions; • Meta-analysis with sensitivity analyses.	**6 RCTs (1627 patients):** • Significant mortality advantage for biomarker-guided therapy: HR, 0.69 (CI, 0.55-0.86) without evidence of heterogeneity. **Conclusions:** *"Titration of therapy incorporating serial BNP or N-terminal pro-B-type natriuretic peptide levels is associated with a significant reduction in all-cause mortality compared to usual care in patients with chronic heart failure."*
He (2009)	**Meta-analysis:** • **What is the predictive value of anemia on clinical outcome of CHF?** • **What is the relationship of anemia severity to left ventricular function or hospitalization?** • Multiple databases, inception-2007;	**20 articles reporting on 20 studies (97,699 patients):** • 18 high-quality studies; others, inadequate descriptions of FU; • No significant publication bias; • Anemia associated with higher risk for death (RR, 1.66; P<.0001); • Anemic patients had more advanced NYHA class (III or IV: RR, 1.35; P<.001) and lower LVEF (WMD, -0.53; P<.0001);

Citation	Design/methods	Results/Conclusions
	• Englsh-language prospective studies reporting all-cause or cardiovascular mortality or hospitalization for CHF patients not receiving therapies for anemia; • Excluded: single cases, reviews, abstracts; • Quality assessment by Jaddad scale; • Tests for heterogeneity and publication bias.	• Severity of anemia closely related to rates of mortality and hospitalization. **Conclusions:** *"Anemia is associated with and increased risk of mortality and rate of hospitalization for heart failure. Anemia is an independent risk factor for adverse outcomes in patients with CHF."*
Hill (Cochrane; 2009)	**Evidence for effect of transfusion thresholds on use of allogeneic and/or autologous blood on clinical outcomes:** • Multiple databases and hand-searching reference lists, inception-2009; • RCTs with patients randomized to restrictive Vs liberal thresholds/triggers (Hb or HCT level below which RBCs would be administered; • Quality assessment and pooling by Cochrane methods	**10 RCTs (1780 patients):** • Restrictive transfusion strategies reduced risk of receiving transfusion by relative 42% (RR, 0.6=58; CI, 0.47-0.71); mean absolute risk reduction, 40% (CI, 24%-56%); • Volume RBCs received reduced by 0.93 units (CI, 0.36-1.5 units); • Heterogeneity among trials was significant for transfusion utilization outcomes (P<0.00001); • Mortality, rates of cardiac events, and LOS were unaffected; • Trials were of poor methodological quality. **Conclusions:** *"The limited published evidence supports the use of transfusion triggers in patients who are free of serious cardiac disease. However, most of the clinical outcomes were generated by a single trial. The effects of conservative transfusion triggers on functional status, morbidity and mortality, particularly in patients with cardiac disease, need to be tested in further large clinical trials In countries with inadequate screening of donor blood, the data may constitute a stronger basis for avoiding transfusion with allogeneic red cells."* .
Tehrani (2009)	**To examine effects of ESA (darbepoetin) in HF patients with anemia:** • PubMed, 1966-2008; • English-language controlled studies; • Analysis by Cochrane software.	**7 studies (663 patients):** • 4 single center, 3 multi-center RCTs; • Most patients in both arms also received iron therapy; • ESA improved cardiovascular measures: hemoglobin (2.35; CI, 1.76-2.93; P < 0.00001); exercise duration (0.91; 0.08-1.7; P=0.03); NYNA functional class (-1.46l -2.32—0.60; P = 0.00009);6-minute walk test (1.42l 0.31-2.54; P= 0.01); B-type BNP(-0.54;-1.03- -0.06; P = 0.03); peak oxygen consumption (0.93; 0.52-1.34;l < 0.00001). **Conclusions:** *"In patients with heart failure and anemia, ESA therapy appears to have a positive effect on several important cardiovascular parameters compared to control therapy. Large RCTs are warranted to comprehensively evaluate the potential effects of ESAs on clinical outcomes."*

Citation	Design/methods	Results/Conclusions
Marik (2008)	**What is the association between RBC transfusion and morbidity/mortality in high-risk hospitalized patients?** • Multiple databases, 1966- June 2007; • "relevant studies" in any language reporting impact of RBC transfusion on clinical outcomes.	**48 reports on 45 observational studies:** • 272,596 patients (median 687/study, range 63-78,974); • Settings: trauma; general surgery; cardiac surgery; neurosurgery; orthopedic, cardiac, or general ICU; • No study reported use of leuko-depleted blood; • In 42 of 45 studies risks outweighed benefits; ratio neutral in 2 studies; in favor of benefit in subgroup (elderly patients with AMI and HCT< 30%) in 1 study; • 17/18 studies: transfusion was independent predictor of death (pooled OR, 1.7; CI, 1.4-1.9); • 22/22 studies independent predictor of infection (pooled OR1.9; CI, 1.5-2.2); • Risk of multi-organ dysfunction syndrome: OR, 2.5 (CI, 1.6-3.3). **Conclusions:** *"Despite inherent limitations in the analysis of observation studies, or analysis suggests that in adult intensive care, trauma, and surgical patients, RBC transfusions are associated with increased morbidity and mortality and therefore, current transfusion practices may require reevaluation. The risks and benefits of RBC transfusion should be assessed in every patient before transfusion."*
Groenveld (2008)	**Effect of anemia on mortality in chronic heart failure (CHF):** • Medline, -November 2007; • English-language studies assessing association between anemia (defined by criteria in primary studies(and mortality in CHF;	**34 studies (153,180 patients):** • 37,2% of patients were anemic; • After minimum FU of 6 months: 46.8% of anemic Vs 29.5% non-anemic patients died: crude OR, 1.96 (CI, 1.74-2.21p<0.001; • Lower baseline hemoglobin values were associated with crude mortality rates: r = -0.396, p = 0.025; • Adjusted HR: 1,467 (CI, 1.26-1.69p p<0.001); • Subgroup analyses: NS difference for anemia mortality risk in diastolic or systolic CHF. **Conclusions:** *"Anemia is associated with an increased risk of mortality for both systolic and diastolic CHF. Anemia should, therefore, be considered as a useful prognosticator, and therapeutic strategies aimed to increase hemoglobin should be investigated."*
Van der Meer (2008)	**ESA treatment of anemia in CHF patients:** • Multiple databases, -July 2008; • English-language RCTs comparing ESAs in anemic adults with CHF to placebo or usual care;	**7 studies (650 patients; range/study, 23-319):** • 363 patients received ESAs, 297 placebo; • 6 studies excluded patients with significant real disease; 3 studies (516 patients)excluded patients with malignancies, on chemo- or radiation therapy; • Average baseline hemoglobin:, 10.3g/dL-11.5g/dL;

Citation	Design/methods	Results/Conclusions
	• Reporting: all-cause mortality; hospitalization venous thrombosis (DVT or pulmonary); or hypertension; • Excluded: FU < 3 months or including patients ≤ 18 yrs. • Quality assessment by USPSTF criteria.	• No studies terminated prematurely; • All-cause mortality (all studies):NS difference; • Significantly reduced hospitalization risk: RR, 0.=59; CI, 0.41-0.86; P = 0.0006; • NS differences for thrombosis or hypertension; • Meta-analysis precluded for left ventricular function. **Conclusions:** *"Among CHF patients, treatment with ESAs is not associated with a higher mortality rate or more adverse events, whereas a beneficial effect on HF hospitalization was seen. These outcomes are in contrast with studies in cancer and kidney disease and support a large morbidity and mortality trial in anemic CHF patients."*
Smith (2006)	**Prevalence of renal failure and mortality risk in HF:** • Medline, -May 2005; • Studies analyzing association between renal impairment and mortality in HF (hospitalized and non-hospitalized); FU≥ 1 yr.	**16 studies (80,098 patients):** • 63% had any renal impairment (creatinine> 1.0mg/dl, creatinine clearance or eGFR< 90 ml/min or cystatin-C> 1.03mg/dl); all-cause mortality increased (HR, 1.56; CI, 1.53-1.80; P<0.001; • 51% had for moderate to severe impairment (HR, 2.31; CI, 2.18-2.44; p<0.001); • Mortality worsened incrementally across range of renal function: 15% (14-17%) increased risk for every 0.5mg/dl increase in creatinine and 7% (4-10%) increased risk for every 10mlmin decrease in eGFR. **Conclusions:** *"Renal impairment is common among HF patients and confers excess mortality. Renal function should be considered in risk stratification and evaluation of therapeutic strategies for HF patients."*
)Jones (2005)	**Benefits of epoetin alpha for left ventricular function and mortality:** • Cochrane methods, Jan 1985-Oct 2000; • No language or study design restrictions; • Included: epo in≥ 10 adult patients/study group; • Question-specific meta-analyses: Epo and LV function; LV hypertrophy and cardiac outcomes.	**26 studies (407 patients):** • Baseline: mean Hb and Hct well below target levels; measures of LV mass and size relatively high; • Pooled estimates of change: consistent demonstration of substantial mean increases in Hb (3.2g/dL range, 2-5 g/dL;42% from baseline) and Hct (9.9%; range,4-16%; 47% from baseline); but significant heterogeneity between studies; • Changes in LV mass: 42g (range, 0-100 g); 15%; body-surface standardized mass decreased overall, 26.7 g/m^2 (0-70g/m^2); • 3 significant relationships between change in Hb: target Hb; duration of disease; duration of FU; • Risk models: LV hypertrophy is strongly and positively associated with cardiovascular and all-cause mortality; LV mass regression is associated with lower incidence of

Citation	Design/methods	Results/Conclusions
		cardiovascular morbidity/mortality. **Conclusions:** *"LVH is common in patients with chronic renal failure and congestive heart failure. Current findings indicate epoetin alfa therapy results in anemia amelioration, as evidenced by higher Hb and Hct levels and reduction of key LVH parameters. LVM regression is associated with lower incidence of cardiovascular morbidity ad mortality, therefore epoetin alfa may provide a survival benefit."*
Taylor (Cochrane; 2005)	**Effectiveness of disease management interventions (clinical service organization interventions:** • Multiple databases, inception-July 2003; hand searching; consultation with experts; • RCTs comparing disease management interventions (multidisciplinary team, case management, monitoring after discharge by phone or home visit) specifically directed at patients with CHF Vs usual care.	**16 RCTs (1627 patients):** • Considerable overlap among classes of interventions although components, intensity and duration varied; • Case management associated with reduced but NS all-cause mortality: OR, 0.86; CI, 0.67-1.10; P = 0.23; evidence stronger when analyses restricted to better quality studies (OR, 0.68; CI, 0.46-0.98; P = 0.04); • Weak evidence that case management reduced admissions for heart failure; but which components of case management are effective is unclear; • Single RCT for multidisciplinary team: reduced HF-related admissions in short term; • Little evidence for clinic-based/FU interventions. **Conclusions:** *"The data from this review are insufficient for forming recommendations.. Further research should include adequately powered, multicenter studies. Future studies should also investigate the effects of intervention on patients' and carers' quality of life, their satisfaction with the intervention, and cost-effectiveness."*

Table 3. Subsequently published studies eligible for Table 1 reviews

Reference	Study design/Methods details/setting	Results/comments
Adams (2009)	**STAMINA registry:** • Prevalence of anemia and relationship of Hb to QoL in HF; • Anemia by WHO definitions; • Random selection of patients (matched non-participant selection described but not analyzed) from community specialty clinics/cardiologists, 6/2002-7/2003; • Participants: ≥ 18 yrs; identified by random selection algorithm; symptomatic HF (fluid retention or shortness of breath); • Excluded: major surgery within 4 weeks after entry; post-organ transplant; participant in clinical trial; anemia secondary to cancer or other non-HF cause; • FU according to managing physician.	**1076 /total 1082 registry patients had complete data for anemia:** • Overall: 41% female; 73% white; mean age 64±14 yrs (68±13 in community; 57±14 in specialty sites); • 1076 subjects for anemia prevalence: mean Hb, 13.3±2.1g.dL; anemia by WHO in 34%; 40% of those > 70yrs. **Conclusions:** *"Findings from the STAMNINA-HF Registry suggest that anemia is a frequent comorbid condition in unselected outpatients with heart failure even when they are well managed with evidence-based therapy. Importantly, age is a readily available and simple marker of risk for anemia, which becomes even more common in patients > 70 years old. The well-established association between anemia and adverse outcomes and the findings in this study support further investigation concerning the importance of anemia as a therapeutic target in patients with heart failure."*
Garty (2009)	**Cross-sectional survey:** • National hospital-based HF survey; • All patients admitted to cardiology or internal medicine wards with HF (fluid retention o; • 25 public hospitals in Israel, 2003.	**4102 patients:** • 2335 with ADHF, of whom 166 (7.1%) received transfusion; • Transfused patients older (75.6% Vs 73.6%; P = 0.4); more likely female (54,8% Vs 43.9%; P = .007); to have diabetes (59.0% Vs 51.1%; p = .04) ;renal dysfunction (59.0% Vs 40.2% P <.001); and to receive inotropes (16.9% Vs 8.0%; P<.001); • Similar rates of ACS and prior HF; • Nadir hemoglobin < 1g/dL (OR, 1.85; CI 1.15-2.96); • 15 transfused patients had bleeding complications, 10 of which were major; • Major predictors of transfusion: ACS (OR, 1.85; CI, 0.14-0.22); inotrope use (OR 2.36; 1.22-4.55); nadir hemoglobin (OR, 0.18ag/dL increase; 1.14-0.22); • In hospital, 30-day, 1- yr, 4-yr mortality higher for transfused patients; • 103 propensity-matched pairs: short term mortality lower with transfusion. **Conclusions:** *"Acute decompensated HF patients receiving transfusion had worse clinical features and unadjusted outcomes, but transfusion per se seemed to be safe and perhaps even beneficial."*

Reference	Study design/Methods details/setting	Results/comments
Pfisterer (2009)	**TIME-CHF RCT:** • 18 mo outcome with BNP-guided Vs symptom-guided therapy; • Both groups stratified by age (60-74 and ≥75); • Sample size basis reported; • Randomization by concealed central allocation in blocks of 8 patients; • Elderly (>60) CHF patients with dyspnea; • 15 centers in Germany and Switzerland; • Single blind (patients but not physicians); • outpatient FU at 1, 3, 6, 12, 18 months; • Treatments adjusted at all but last visit to achieve targets by 6 months (up-titration phase to guideline based NYHA class ≤ II), then observation for one yr; • All patients followed for BNP levels but only BNP group MDs received results.	**622 randomized:** • Similar rates of survival free of all-cause hospitalization: 41% (BNP) Vs 40% (symptom);HR, 0.91; CI, 0.72-1.15; P = .39; • QoL improved over 18 mo FU but improvements similar; • Survival free of hospitalization higher for BNP: 72% Vs 62%; HR, 0.68 (CI, 0.50-0.92); P = .01; • BNP –guided therapy improved outcomes for 60-75 yrs but not >75 (P> .02 for interaction). **Conclusions:** *"Heart failure therapy guided by N-terminal BNP did not improve overall outcomes or quality of life compared with symptom-guided treatment."*
Tehrani (2009a)	**Cross-sectional:** • HF patients with preserved systolic function (LVEF≥0.50); • 2 groups: #1, anemic at baseline (Hb< 12g.dL in women, < 13g/dL in men; #2 not anemic; • Multivariate regression analyses: impact of Hb on 5-yr hospitalization or mortality rates;	**294 patients:** • 162 with anemia (#1), 132 without (#2); • Anemic patients had shorter mean survival (37.8±1.8 Vs 44.9±1.8 months; P=0.01); • NS difference in hospitalization rates; • Subgroup analyses: anemia was significant predictor of mortality in patients > 75 yrs with diastolic failure (P= 0.081). **Conclusions: "***We found that anemia is associated with increased long-term mortality rates in patients who have diastolic heart failure. In addition, anemia appears to be an independent predictor of worse outcomes in elderly heart failure patients."*
Go (2006)	**Cross-sectional:** • Hb, kidney function, and adverse events (death, hospitalization) in HF; • Kaiser-Permanente (N CA)1996-2002; • Longitudinal outpatient Hb, creatinine and GFR from K-P records; • Mortality from state death records.	**59, 722 adults with HF:** • 46% female; mean age 72; • Compared with Hb levels 213.0-213.9g/dl, multi-variable-adjusted risk for death increased with lower Hb: Hb 12.0-12.9, HR, 1.5(CI, 1.44-1.57); HB 11.0-11.9, HR, 1.89(1.80-1.98); Hb 10.0-10.9 (HR, 2.31; 2.18-2.45); Hb 9.0-9.9 (HR, 2.31; 2.18-2.45, Hb< 9.0 (HR 2.44; 2.28-2.61); • Hb ≥17.0 (HR, 1.42; 1.24-1.63); • Compared with GFR≥60 ml/min, those with GFR< 45ml/min: HR, 1.39 (1.34-1.44):< 44 (HR,

Reference	Study design/Methods details/setting	Results/comments
		2.28(2.19-2.39) < 15 (HR, 3.26 ;3.05-3.49); on dialysis (HR, 2.44; 2.28-2.61); • Relations similar for risk of hospitalization; • Findings did not differ by level of LV function; • Hb an independent predictor of outcome at all levels of kidney function. **Conclusions: "***Very high (≥17.0 g/dL) or reduced (< 13g/dL) hemoglobin levels and chronic kidney disease independently predicted risks of hospitalization or death in heart failure, regardless of the level of systolic function. Randomized trials are needed to evaluate whether raising hemoglobin levels can improve outcomes in chronic heart failure."*

IN-PROGRESS RESEARCH

TAP searched www.clinicaltrials.gov on April 29, 2010 using "anemia" and "heart failure". Among the 78 ongoing studies listed, those detailed in Table 3, once published, should help to resolve ongoing issues for anemia in CHF as defined by the reviews included here.

Table 4. In-progress studies for anemia in CHF

Title/design	Sponsor/location	Projected completion (if noted)
IV ferrous sucrose to improve exercise capacity in CHF/RCT	Poland	2006
Erythropoietin alpha for anemia in heat failure with preserved ejection fraction/RCT	Columbia University	2011
IRON-HF (iron supplementation in heart failure patients with anemia/RCT)	Brazil	
RED-HF(reduction of events with darbopoietin alfa in heart failure/RCT)	Amgen/multicenter	2012

CONCLUSIONS AND DISCUSSION

Beyond its role as a predictor of poor outcome, anemia in heart failure is incompletely understood and its value as a therapeutic target uncertain. The searches detailed above did not identify systematic reviews or analytic studies focused on transfusion as an intervention for congestive heart failure published within the last two decades. Recent publications detail the state of knowledge for anemia in heart failure:

> *"Chronic heart failure (CHF) is a leading cause of morbidity and mortality worldwide. Anemia is a common (12-55%) co-morbid condition and is associated with worsening symptoms and increased mortality. Anemia is treatable and can be targeted in the treatment of patients with CHF. Erythropoiesis-stimulating agents (ESA), supported by iron therapy, are used to treat anemia in chronic kidney disease and cancer, however safety concerns have been raised in these patients. The clinical benefit and safety of these agents in CHF remains unclear."* (Ngo, 2010).

> *"There are many questions about anemia in congestive heart failure (CHF)…Is anemia common? How common? Why is anemia increasing in prevalence in CHF? Is it an independent risk factor for mortality, morbidity, and hospitalization?…Does iron treatment improve the anemia and general condition of CHF patients? Is oral iron better than intravenous? Is it worthwhile treating iron deficiency even if anemia is not present? Does correction of anemia with ESAs improve CHF? What is the target hemoglobin (HB) in CHF? Are there dangers to the use of ESA and IV iron? What effect does iron deficiency have on platelet number and function? What effect does an increase in platelets have on inflammation, thrombosis, and atherosclerosis? What are the advantages of using ESA and IV iron alone or in combination in CHF, CKD, and the anemia of cancer chemotherapy?* (Silverberg, 2009).

> … *"For much of the last century, RBC transfusion has been viewed as having obvious clinical benefit. However, over the last 20 years, RBC transfusion has come under increased scrutiny...it is now becoming clear that there are other important, less recognized* (than infection) *risks of RBC transfusion related to RBC storage effects and to*

> *immuno-modulating effects of transfusion which occur in almost all recipients…may increase the risk of nosocomial infection, acute lung injury, and the possible development of autoimmune diseases later in life."* (Marik, 2008).
>
> *"Research into the anemia of heart failure is still in its infancy. We are unsure if it is generally related to a low red cell mass. We are unsure whether it responds to conventional hematinics, the only robust test for hematinic deficiency. We do not know whether treating it will be beneficial or safe. We all hope it will be a new target for treatment that will transform the lives of patients. Imagination and innovation will make important contributions to the field, but they are not substitutes for randomized controlled trials demonstrating efficacy and safety."* (Clark, 2005).

Ongoing, adequately powered randomized controlled trials (RCTs) (Table 4) may resolve some of these uncertainties.

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Table 5: Excluded articles

Citation	Reason for exclusion
Damiani (2010)	Outside charge
Simon (2010)	Intended to include but identified no studies for CHF
Mommersteeg (2009)	Outside charge
Moscucci (2009)	Narrative review
Pagourelias (2009)	Narrative review
Silverberg (2009; 2009a)	Narrative review
De Luca (2007)	Quasi-systematic review
Notebaert (2007)	No studies in CHF patients included
Klein (2006)	Narrative review

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TAP staff person/position	Role	Responsibilities
Karen Flynn Program Manager Boston	Primary author	Conception and conduct of review: • Communication with client; • Clinical search strategy; • Interim information; • Analytic framework; • Draft review; • Final review.
Elizabeth Adams Health System Specialist Boston	Consultation throughout project	• Internal content and format review; • Confirmation of exclusion for unintelligibility.
Elaine Alligood Information Specialist Boston	Literature database searches	Database searches: • Design/conduct technical strategy; • Choose/manage databases; • Strategy text and references for report. • TAP library/archive.
Rebecca Morton Library Technician Boston	Article retrieval	Information retrieval: • Full text from print journals and electronic resources; • Manage reference lists.
Bernard Spence Administrative Officer Boston	Administrative support	• Budget/resources; • "intelligent lay reader" review; • Project tracking.

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